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(54) Title: **PROCESS FOR THE PRODUCTION OF 16,17-[(CYCLOHEXYLMETHYLEN)BIS(OXY)]-11,21-DIHYDROXY-PREGNA-1,4-DIEN-3,20-DION OR ITS 21-ISOBUTYRAT BY TRANSKETALISATION**

(57) Abstract: The invention relates to a process for the preparation of 16,17-[(cyclohexylmethylene)bis(oxy)]-11,21-dihydroxy-pregna-1,4-diene-3,20-dione[11 β ,16 α (R)] and similar compounds, by reaction of an appropriate 16,17-ketal with cyclohexanealdehyde.

PROCESS FOR THE PRODUCTION OF 16,17-(CYCLOHEXYLMETHYLEN) BIS(OXY)-11,21-DIHYDROXY-PREGNA-1,4-DIEN-3,20-DION OR ITS 21-ISOBUTYRAT BY TRANSKETALISATION

Technical field

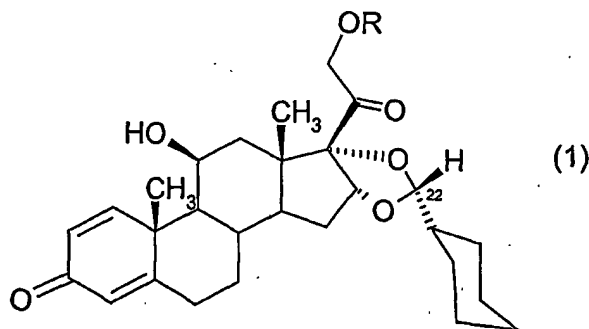
The invention relates to a novel process for the preparation of a known glucocorticoid, which is used in the pharmaceutical industry for the production of medicaments.

Prior art

The International patent application WO 9422899 describes novel prednisolone derivatives and a process for their preparation. In this process, 16-hydroxyprednisolone is reacted with cyclohexanealdehyde. German patent application DE 41 29 535 discloses novel glucocorticoids and a process for their preparation. The process comprises reacting pregna-1,4-diene-3,20-dione-16,17-dihydroxy compounds, in the form of their 16,17-diester derivatives, with aldehydes (e.g. with cyclohexanealdehyde) to give the desired final products.

Description of the invention

The invention relates to a process for the preparation of the compounds of the formula 1,

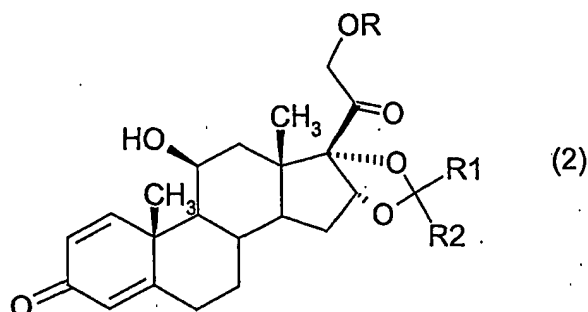


in which

R is hydrogen (H) or isobutyryl $[\text{CO}-\text{CH}(\text{CH}_3)_2]$, in predominantly epimerically pure form.

It has now been found that the compounds of the formula 1 are obtained in a simple manner in good yield and surprisingly high epimeric purity when, rather than the 16,17-dihydroxy compound or the 16,17-diester, the corresponding 16,17-ketal, in particular the 16,17-acetonide derivative, is used as a starting material.

The invention thus relates to a process for the preparation of the compounds of the formula 1 in predominantly epimerically pure form, which comprises reacting compounds of the formula 2,



in which

R is hydrogen (H) or isobutyryl [CO-CH(CH₃)₂],

R1 is 1-4C-alkyl and

R2 is 1-4C-alkyl,

with cyclohexanealdehyde.

Preferably, the process is carried out using those compounds of the formula 2 in which R1 and R2 are in each case methyl (CH₃).

The reaction is carried out in suitable solvents such as, for example, ethers, e.g. dioxane, diisopropyl ether, esters, e.g. ethyl acetate, halogenated hydrocarbons, e.g. methylene chloride, chloroform, nitrated hydrocarbons, e.g. nitromethane, 2-nitropropane or preferably 1-nitropropane, or without solvents, with addition of catalytic or else relatively large amounts of acid, such as mineral acids, e.g. tetrafluoroboric acid or in particular perchloric acid, or sulfonic acids, in particular methanesulfonic acid, at temperatures of advantageously 0°C to 60°C.

The reaction of the 16-hydroxyprednisolone ketal of the formula 2 with cyclohexanealdehyde normally yields an epimer mixture. Surprisingly, the reaction, however, is controlled according to the invention by means of suitable reaction conditions such that the R-epimer desired and indicated in formula 1 results. According to the invention, "in predominantly epimerically pure form" thus means that the R-epimer (based on the absolute configuration at C-22) in the compound 1 where R = hydrogen (H) results to at least 90%, preferably at least 95%, in particular at least 97%, based on the total yield.

For the predominant preparation of the R-epimer, the following conditions, for example, are preferred: as solvents, halogenated hydrocarbons (such as methylene chloride or chloroform) or nitrated hydrocarbons (such as nitromethane, 2-nitropropane or preferably 1-nitropropane) and, as a catalyst, methanesulfonic acid (at temperatures from 10°C to 40°C) or 35-70% strength, in particular 60-70%

strength, perchloric acid (at temperatures from 0°C to 40°C, preferably 15°C to 30°C, in particular 20°C to 25°C).

If the R-epimer is desired in purer form than is achievable on account of the reaction conditions, suitable separation and purification steps – such as, for example, preparative HPLC, or fractional crystallization such as described in international patent application WO 9809982 – may follow the reaction.

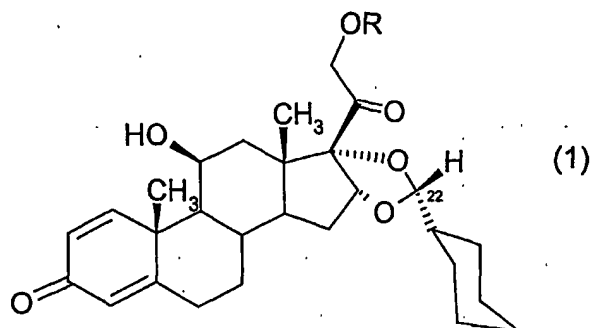
The following example serves to illustrate the invention in greater detail:

Example**16,17-[(Cyclohexylmethylene)bis(oxy)]-11,21-dihydroxypregna-1,4-diene-3,20-dione[11 β ,16 α (R)]**

20 g of desonide are suspended in 70 ml of 1-nitropropane and treated slowly with ice-cooling with 12.6 ml of 70% strength perchloric acid and 6.6 g of cyclohexanecarbaldehyde. The reaction mixture is stirred overnight at room temperature and then filtered. The filter cake is dissolved in 90 ml of DMF and the solution is added dropwise with stirring to sodium hydrogencarbonate solution. The precipitate is filtered off with suction, washed with water and dried. 19 g of the title compound having an R-/ S-epimer ratio of 97.8 / 2.2 are obtained.

Patent claims

1. A process for the preparation of the compounds of the formula 1,

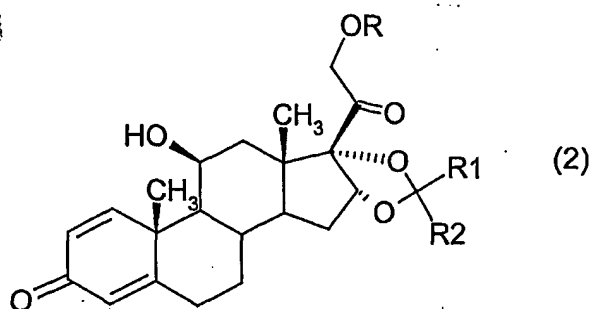


in which

R is hydrogen (H) or isobutyryl [CO-CH(CH₃)₂],

in predominantly epimerically pure form,

which comprises reacting compounds of the formula 2,



In which

R is hydrogen (H) or isobutyryl [CO-CH(CH₃)₂],

R₁ is 1-4C-alkyl and

R₂ is 1-4C-alkyl,

with cyclohexanealdehyde.

2. The process as claimed in claim 1, where R is hydrogen (H).
3. The process as claimed in claim 1, where R is isobutyryl [CO-CH(CH₃)₂].
4. The process as claimed in claim 1, where R₁ and R₂ are in each case methyl (CH₃).

5. The process as claimed in claim 1, wherein a halogenated or nitrated hydrocarbon is used as a solvent.
6. The process as claimed in claim 1, wherein methanesulfonic acid is used as a catalyst.
7. The process as claimed in claim 1, wherein perchloric acid is used as a catalyst.
8. The process as claimed in claim 1, wherein the reaction is carried out at temperatures between 0°C and 40°C.
9. The process as claimed in claim 1 for the preparation of the compound of the formula 1, in which R is hydrogen (H), in over 95 % epimerically pure form, wherein compounds of the formula 2, in which R is hydrogen (H), R1 is methyl (CH3) and R2 is methyl (CH3), are reacted with cyclohexanecarbaldehyde using perchloric acid as a catalyst at temperatures between 0°C and 40°C.

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II nal Application No

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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